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EXAMINER

TURNER, SHARON L

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**BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES**

Paper No. 26

Application Number: 09/207,649  
Filing Date: December 08, 1998  
Appellant(s): LINDQUIST, SUSAN

\_\_\_\_\_  
Gina N. Shishima  
For Appellant

**EXAMINER'S ANSWER**

This is in response to the appeal brief filed 04 November 2002.

**(1) *Real Party in Interest***

A statement identifying the real party in interest is contained in the brief.

**(2) Related Appeals and Interferences**

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

**(3) Status of Claims**

The statement of the status of the claims contained in the brief is incorrect. A correct statement of the status of the claims is as follows:

This appeal involves claims 1, 3, 7-20, 22 and 37. Claims 38-40 are withdrawn from consideration as not directed to the elected invention.

**(4) Status of Amendments After Final**

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

**(6) Issues**

The Appellant's statement of the issues in the brief is substantially correct. The changes are as follows: Issue A should be directed to claims 1, 3, 7, 12-13, and 17-18. Issue B should be directed to claims 1, 3, 12-13, 15, 17, 19 and 37. Issue C should be directed to claims 1, 3, 7, 12-13, 17-18 and 37. Issues D and E are not of issue in the record as set forth in the action of 4-29-02. Accordingly, these are not issues upon which this appeal pertains. Issue F is petitionable to the Commissioner but not appealable to the board. Accordingly, issue F is not an issue upon which this appeal pertains. Issue G omits claim 22, issue G pertains to claims 1, 3, 7-20, 22 and 37. It is noted that p. 24 was omitted in two copies of the Brief. This page contains the

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arguments as to issue G. The Examiner has stapled a copy of the omitted page to the second and third copies of the Brief before the Board. Issue H is moot as the rejection has been withdrawn. The Patino sequences are not of mammalian origin. Issues I-J are correct as set forth in the issues on appeal. However, issues I and J no longer rely on Patino.

**(7) Grouping of Claims**

Appellant's brief includes a statement that particular claims do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

**(8) Claims Appealed**

The copy of the appealed claims contained in the Appendix to the brief is correct.

**(9) Prior Art of Record**

✓ Hughes et al., "Two-hybrid system as a model to study the interaction of beta-amyloid peptide monomers" PNAS, vol 93 (05 March 1996), pp.2065-70.

✓ 5,854,204 Findeis et al., 29 December 1998

— WO 91/04339 Cordell et al., 04 April 1991

— Phizicky et al., "Protein-protein interactions: Methods for detection and analysis" Microbiol. Reviews, vol 59 (March 1995), pp. 94-123.

— King et al., "Prion-inducing domain 2-114 of yeast Sup35 protein transforms in vitro into amyloid-like filaments" PNAS vol 94 (June 1997), pp. 6618-22.

— Patino et al., "Support for the Prion hypothesis for inheritance of a phenotypic trait in yeast" Science, vol 273 (02 August 1996), pp. 622-626.

~~Selvaggini et al.~~, "Molecular characteristics of a protease-resistant amyloidogenic and neurotoxic peptide homologous to residues 106-126 of the prion protein" Biochem. Biophys. Res. Comm., vol 194 (16 August 1993), pp. 1380-1386.

~~Ogawa et al.~~, "Localization, trafficking and temperature-dependence of the Aequorea green fluorescent protein in cultured vertebrate cells" PNAS, vol 92 (December 1995), pp. 11899-11903.

~~Schilthuis et al.~~, "Chimeric retinoic acid/thyroid hormone receptors implicate RAR-alpha1 as mediating growth inhibition by retinoic acid" EMBO J., vol 12 (1993), pp. 3459-66.

~~Mohler et al.~~, "Membrane-bound neomycin phosphotransferase confers drug-resistance in mammalian cells: A marker for high-efficiency targeting of genes encoding secreted and cell-surface proteins" Somatic Cell & Mol. Genetics, vol 20 (1994), pp. 153-62.

**(10) Grounds of Rejection**

The following ground(s) of rejection are applicable to the appealed claims. The issues are set forth in the order (A-J) presented in the Brief:

Issue A, claims 1, 3, 7, 12-13, and 17-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Hughes et al, PNAS, 93:2065-70, 1996. This rejection is set forth in prior Office Action, Paper No. 23, mailed 04/29/02.

As set forth therein, Hughes et al teach claim 1, a yeast-two hybrid system as a method of identifying amyloid aggregation and aggregating domains which are capable of inhibiting amyloid aggregation, see abstract and Discussion, page 2068-9 and Figure

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1. In these experiments Hughes identifies candidate substances (mutated forms of amyloid or alternate proteins) which inhibit the self-aggregation of amyloid peptides. Hughes explains that the kinetics of amyloid fibril formation by beta-amyloid is typical of a nucleation-dependent polymerization mechanism. This event was studied by investigating the interaction of monomers recognized by Hughes as nucleation-dependent aggregation which leads to fibril formation as depicted in Figure 1 and abstract, see in particular lines 1-5 and 13-30. Claim 3 is anticipated by Hughes et al as the aggregate-prone protein comprises -amyloid chimeric proteins (LexA-A fusion and B42-A fusion, see Experimental Procedures). Claim 7 is anticipated as the chimeric protein comprises at least an aggregate forming domain and defines at least residues 19 and 20 as a domain critical to such aggregate formation of a mammalian amyloid polypeptide, operably attached to a detectable marker protein. The marker protein is the bait and prey constructs which lead to the expression of reporter plasmids LEU2 and lacZ genes as disclosed at p. 2067, column 1-p. P. 2068 column 2, growth with leucine Beta-galactosidase. Claims 12-13 are anticipated as the amyloid polypeptide is -amyloid and comprises at least about amino acids 1-42. Claims 17-18 are anticipated as the aggregate is labeled with a chromophore (ECL detection, see Experimental procedures).

Issue B, claims 1, 3, 12-13, 15, 17-19 and 37 stand rejected under 35 U.S.C. 102(b) as being anticipated by Cordell et al, WO91/04339, 4 April, 1991. This rejection is set forth in prior Office Action, Paper No. 23, mailed 04/29/02.

As set forth therein, Cordell et al teach assays and reagents for amyloid deposition including the identification of agents that inhibit amyloid formation. It is noted at p. 8, lines 20-34 that within the scope of the invention is modified beta amyloid

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proteins with one or more substituted amino acids. Thus as the specification defines chimeric proteins as non-naturally occurring, the substituted mutants apply as chimeric aggregate-prone amyloid proteins. The amyloid products produced may be expressed in yeast and include beta-amyloid 1-42 and preamyloid precursors, see in particular p. 6, lines 5-30 and p. 7, line 13 and p. 11, lines 3-28. The methods include screening compounds for inhibition of aggregate formation and the amyloid aggregates are detected by Congo red, thioflavin S or silver salt staining which are indicative of fibrillary material, in particular p. 13, lines 20-36. Aggregates may be detected by attachment of antibodies or other labels such as fluorescent enzymatic or radioactive (<sup>35</sup>S) labels, in particular, pps. 14-15, especially p. 15, lines 5-6 and 19-20. Thus, the reference teachings anticipate the claimed invention.

Issue C, claims 1, 3, 7, 12-13, 17-18 and 37 are rejected under 35 U.S.C. 102(e) as being anticipated by Findeis et al., US Patent No. 5,854,204 filed 3-14-1996. This rejection is set forth in prior Office Action, Paper No. 23, mailed 04/29/02.

As set forth therein, Findeis et al., teach A-beta peptides including chimeric peptides as defined in the specification which differ from naturally occurring beta amyloid at one or more amino acids residues and including aggregating domains which are aggregating portions of beta-amyloid. Findeis also teach screening assays using such peptides to identify modulatory influences on amyloid aggregation, see in particular Abstract. The peptides are expressed in yeast cells in particular *S. Cerevisiae* as discloses at col. 38, lines 5, 12 and 60-65. The peptides may also be fusion proteins or chimeras as disclosed in the paragraph spanning columns 30-31. The proteins may be detected or labeled by biotinylation, labeled by fluorescence, or monitored in seeded assays, see in particular columns 31-33 and Example 6. The

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peptides include those of Tables I-VI and Examples 1-12 in particular. Thus the reference teachings anticipate the claimed invention

Issues D-F are not issues under appeal.

Issue G, claims 1, 3, 7-20, 22 and 37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is set forth in prior Office Action, Paper No. 23, mailed 04/29/02.

As set forth therein, the terms "aggregate-prone amyloid peptide" and "aggregate-prone amyloid protein" as used in claim 1 are indefinite because the recitations are not the same and the artisan cannot readily discern the difference, if any in the scope of the two terms. As peptides are generally but not necessarily smaller in length than proteins or polypeptides, and the specification fails to define the different terms, it is unclear whether or not the "peptides" or "proteins" are the same or are of different scope, i.e., are different in sequence and/or length.

The terms "-amyloid polypeptide", "-amyloid", and "-amyloid protein" as used in claims 1, 3, 7 and 12-14, are indefinite because the recitations are not the same and the artisan cannot discern the difference in scope between the terms. As there are multiple "amyloid" peptides of various sequences and lengths recognized in the art, and the terms are not defined in the specification, the artisan can not discern the metes and bounds or difference in scope of the various recitations.

In addition, while applicant may be his or her own lexicographer, a term in a claim may not be given a meaning repugnant to the usual meaning of that term. See *In re Hill*, 161 F.2d 367, 73 USPQ 482 (CCPA 1947). The terms "amyloid protein/peptide"



, "aggregated amyloid formation", "aggregation" and "chimeric" in the claims are used by the claims to mean (roughly), any non-naturally occurring peptide which either forms amyloid or amyloid-like deposits, i.e., for example, is insoluble under physiological conditions, or which shares the characteristics of specific embodiments of the specification for example exhibiting a shift in spectral analysis as noted in Figures 1-2 and 4 for Sup35, while the accepted meaning is aggregated formation of amyloid proteins or amyloid fusion proteins, i.e., of amyloid peptides.

The term "aggregated amyloid formation" and "aggregation" as used in the claims are further indefinite because the specification's discussion of the terms include solubility, being "amyloid-like" or "amyloidogenic", see p. 5, lines 10-23, but such exemplary embodiments do not establish or define the interactions or conditions which are required for "aggregation" to occur. For example the recitation could indicate insolubility, spectral shift, self-binding or binding to an alternative peptide. It is noted that even the art recognizes various forms of amyloid fibril aggregation, see in particular Newcombe et al., *Biochimica et Biophysica Acta*, 104:480-486, 1965, Cordell et al., Hughes et al., and Findeis et al., of record, but as previously set forth the peptides which are aggregating are not even required to be amyloid peptides, and thus the artisan is left with no guidance as to the specific interaction which is required to occur. The specification fails to delineate that which is "amyloid-like" and thus the artisan could not readily discern any of the characteristics of amyloid protein interactions amongst those known, are sufficient or required. Thus, the artisan can not readily determine the metes and bounds of the claims based on the prior art and the guidance provided in the specification and therefore clarification of the precise structural and or functional features and interactions is required.

Further, chimeric peptides are recognized in the art as fusion proteins. However, the specification describes "chimeric" peptides as "peptides that do not naturally occur together in a single peptide unit", see p. 5, lines 25-p.6, line 23 and thus the term alternatively encompasses any non-naturally occurring sequence, for example a mutated peptide by deletion, insertion or substitution which is not necessarily a fusion protein as recognized by the fusion of two known naturally occurring compounds to make a single non-naturally occurring compound..

Further compounding the indefinite nature of the claims is the recitation of an "aggregate forming domain" as claimed in claim 7. Proteins comprising an "aggregate forming domain" are loosely described in the specification at p. 5, line 25 - p. 6, line 13. Yet, the specification fails to provide the structural constraints of the domain and fails to clarify the functional requirements of the required "aggregation". For example, the domain may reference those peptide residues specifically bound to each other in the aggregate or may specify those regions which are protease resistant.

Thus, for the aforementioned reasons the skilled artisan cannot discern the metes and bounds, structural and functional limitations of the claims and clarification, in different terms is required.

Issue H, is now moot as the rejection is withdrawn. The Patino sequences are not of mammalian origin.

Issue I, claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over either Hughes et al, PNAS, 93:2065-70, 1996, Cordell et al, WO91/04339, 4 April, 1991, or Findeis et al., US Patent No. 5,854,204 filed 3-14-1996 as set forth above in view of either King et al., PNAS, 94(13):6618-22, June 24, 1997, or Selvaggini et al., Biochem.

& Biophys. Res. Comm., 1993 Aug 16, 194(3):1380-86. This rejection is set forth in prior Office Action, Paper No. 23, mailed 04/29/02.

As set forth therein, Hughes et al., Cordell et al., Findeis et al., and Patino et al., are as set forth above and teach the method of claim 1.

Neither Hughes et al., Cordell et al., nor Findeis et al., teach the limitations of claim 16, the method of claim 1 wherein aggregation is detected by increased protease resistance.

King et al., and Selvaggini et al., each teach analysis of aggregation of aggregate prone amyloid proteins via protease resistance, see in particular Abstracts of both articles.

Thus, it would have been prima facie obvious to the skilled artisan that one could practice the method of claim 1 as taught by Hughes, Cordell, or Findeis with the modification of detecting aggregation via protease resistance as taught by either King or Selvaggini. One of skill in the art would have been motivated to make such modification based on the ease of the assay and expectation of positive results using the assay as taught by King and Selvaggini. Thus, the cumulative reference teachings render the invention obvious.

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Issue J, claims 9-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Hughes et al, PNAS, 93:2065-70, 1996 or Findeis et al., US Patent No. 5,854,204 filed 3-14-1996 as set forth above in view of the cumulative teachings of Ogawa et al., PNAS 92(25):11899-903, 1995, Schilthuis et al., EMBO Journal, 12(9):3459-66, 1993 and Mohler et al., Somatic Cell & Mol. Genet., 20(3):153-62, 1994. This rejection is set forth in prior Office Action, Paper No. 23, mailed 04/29/02.

As set forth therein, Hughes et al., Findeis et al., and Patino et al., are as set forth above and teach the method of claims 1 and 7.

Neither Hughes et al., nor Findeis et al., et al., teach the limitations of claims 9-11, the method of claim 7 and 10 wherein the marker proteins are a drug-resistance marker protein, a hormone receptor protein and a glucocorticoid receptor protein.

Ogawa et al., teach a chimeric fusion marker protein marker where detection is achieved using green fluorescent protein linked to glucocorticoid receptor as a marker of dexamethasone induced translocation to the nucleus, see in particular Abstract.

Schilthuis et al., teach a chimeric fusion protein marker where detection is achieved using the thyroid hormone receptor for detection via transcription activation with thyroid hormone T3, see in particular Abstract.

Mohler et al., teach a chimeric fusion protein marker where detection is achieved using the gene for membrane-bound neomycin phosphotransferase for the conferrance of drug resistance, see in particular Abstract.

Thus, it would have been prima facie obvious to the skilled artisan that one could practice the method of claims 1 and 7 as taught by Hughes or Findeis with the modification of a chimeric fusion marker protein for the glucocorticoid receptor as taught by Ogawa, the thyroid hormone receptor as taught by Schilthuis or a drug resistance

marker protein as taught by Mohler for the detection marker of aggregation. One of skill in the art would have been motivated to make such modification based on the detection achieved and expectation of positive results using the detection assays as taught by the cumulative teachings of Ogawa, Schilthuis and Mohler. Thus, the cumulative reference teachings render the invention obvious.

**(11) *Response to Argument***

Issue A, Appellants argue that the Hughes reference pertains to the interaction of monomers and that such interaction does not constitute aggregation. Appellants refer to specific passages at p. 2065, column 2 and p. 2070, column 1 and conclude that the interaction of two monomers is necessary prior to the aggregation of multiple monomers and that the artisan would not interpret the term "aggregation" to include the interaction of two individual monomers. Appellants argue that the specification does not define "aggregation" to include the interaction of monomers. Appellants argue that no evidence of record supports the interaction of two monomers as aggregation. Appellants argue that the Examiners reference to Figure 1 does not constitute substantial evidence. Appellants argue that Findeis, column 8, lines 11-16 uses the term "aggregation" to describe the interaction of multiple peptides and not between just two peptides. Appellants argue that the conditions of Hughes are not "under conditions effective to allow aggregated amyloid formation" as Figure 1 refers to the interaction of monomers and the specification at p. 5, lines 18-19 references that "amyloid or amyloid like deposits are generally insoluble fibrillary material" and that thus the monomer assay

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of Hughes would not be performed under such conditions. Appellant argues that Hughes also provides no suggestion of suitable conditions to promote aggregate formation.

In response, Hughes at p. 2065 and p. 2070 makes clear that the study of issue is designed to function as an indication of aggregate formation. At p. 2065, last sentence of the abstract Hughes states that "The findings presented in this paper suggest that the two-hybrid system can be used to study the interaction of Abeta monomers and to define the peptide sequences that may be important in nucleation dependent aggregation." At p. 2070, Hughes states that "the slow and thermodynamically unfavorable interactions between individual monomers may be the rate-limiting step in aggregation." Thus, in contrast to Appellant's interpretation the Examiner notes that these passages apparently refer to the earliest forms of aggregation as that between two monomers. While many forms of aggregation are recognized as evidenced in the art and Appellants specification, there is no provision for importing a specific meaning for aggregation as interaction of more than two monomers. The specification is silent as to the particular interaction which is necessary for an aggregate to be formed. Example 6 of Findeis teaches nucleation and seeded assays to measure beta-amyloid aggregation. The assay is disclosed as being concerned with "the lag time observed prior to nucleation, after which the peptide rapidly forms fibers as reflected in a linear rise in turbidity." Consistent with Hughes, the interaction of monomers is hypothesized as being the nucleation event and thus it is apparent from the art that aggregation begins with the formation of two monomers.

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Appellants and the art appear to recognize that monomer interaction forms an aggregate as such is measured via circular dichroism, seeded assays or nucleation dependent assays as disclosed in the specification, Findeis and Hughes. While the art recognizes more complex aggregates than simple aggregations of two monomers, there is no such limitation in the claims that require greater than two monomeric forms. Thus, Appellants arguments are insufficient to import a definition of an aggregate as requiring more than two monomers. In regard to the appropriate conditions effective to allow aggregated amyloid formaion, the conditions of Hughes are deemed sufficient as the interaction of two monomers occurs and there is no limitation as to those conditions which are sufficient as set forth in the specification or claims. Thus, the rejection is maintained for the reasons of record.

Issue B, Appellants argue that a chimeric protein as defined in the specification fails to encompass substituted peptides as taught by Cordell. In particular Appellants specification defines at p. 5, lines 26-27 a chimeric protein to mean that the protein comprises polypeptides that do not naturally occur together in a single protein unit. Appellants suggest their use of plural form means at least two separate polypeptides combined. Appellants appear to argue that a modified protein cannot be considered to be two different peptides combined to form a non-naturally occurring polypeptide. In contrast, amino acid substitutions within a known peptide are non-naturally occurring. The two different segments constitute the joining of two separate polypeptides. Cordell encompasses various mutations including of N and C' terminally modified sequences,

see in particular pp. 7-9 and sequences with one or more substitutions. Thus, as defined there is no apparent reasoning for the peptides of Cordell to not meet the claim limitations. The interpretation is only as broad as the language and definitions used in the specification to construct it.

Issue C, Appellants argue that Findeis does not teach performing the screening assay in yeast with reference to Example 5. However, Findeis does teach expression of the peptide modulators via recombinant DNA technology in yeast, see in particular col. 38, lines 5, 12 and 60-65 as previously set forth. Findeis also teaches fusion or chimera proteins as disclosed in the paragraph spanning columns 30-31. Just because an exemplary assay uses synthesized material does not preclude the use of the recombinantly made material as expressly taught in the Findeis specification, in particular where the peptide may be a fusion or chimera. The conditions are met as neither the specification nor claims limit the conditions to particular conditions and as evidenced by the examples, amyloid aggregates are differentially formed in the presence or absence of particular modulators.

Issue G, Appellants argue that the "protein" includes the "peptide" and that there is no basis for an indefiniteness rejection based upon such language. It is noted that the rejection of a) as set forth in the action was between aggregate-prone amyloid polypeptide and aggregate-prone amyloid peptide. Nevertheless, the artisan does not necessarily and immediately recognize the differences in length apparently intended to be described by the different terms as used in the claim, in particular to the different



usage of polypeptide and peptide as in a) or between beta-amyloid polypeptide, beta-amyloid and beta-amyloid protein as in b). Appellants argue in a) that the terms are different but in b) that they are synonymous. Yet the artisan cannot clearly perceive Appellants intentions as the same terms are used differently in various instances of the claims. Thus, no clear meaning is established to interpret the claims. In c) Appellants argue that the terms are not repugnant. 'Repugnant' is a term recognized within the MPEP, see in particular MPEP 2111.01, 706.03, form paragraph 7.34.02 and 608.01(o). Repugnant use describes the use of a word to mean other than it's normally recognized meaning. As set forth in the rejection, the terms of interest include "amyloid protein/peptide", "aggregated amyloid formation", "aggregation" and "chimeric". As used in the specification, the terms reference any non-naturally occurring peptide which either forms amyloid or amyloid-like deposits. An amyloid or amyloid-like deposit may be any approximating a property of a recognized amyloid aggregate, i.e., for example if an aggregate is insoluble under physiological conditions, or exhibits a shift in spectral analysis as noted in Figures 1-2 and 4 for Sup35. In contrast, the art accepted meaning of amyloid protein or peptide is generally limited to specific amyloid sequences and not to any sequences that approximates its aggregated formation.

The term "aggregated amyloid formation" and "aggregation" as used in the claims are further indefinite because the specification's discussion of the terms include solubility, being "amyloid-like" or "amyloidogenic", see p. 5, lines 10-23, but such exemplary embodiments do not establish or define the interactions or conditions which are required for "aggregation" to occur. For example the recitation could indicate insolubility, spectral shift, self-binding or binding to an alternative peptide. It is noted that even the art recognizes various forms of amyloid fibril aggregation, see in particular Newcombe et al., *Biochimica et Biophysica Acta*, 104:480-486, 1965, Cordell et al.,

Hughes et al., and Findeis et al., of record, but as previously set forth the peptides which are aggregating are not required to be amyloid peptides, and thus the artisan is left with no guidance as to the specific interactions which are required to occur. The specification fails to delineate that which is "amyloid-like" and thus the artisan could not readily discern any of the characteristics of amyloid protein interactions amongst those known, that are sufficient or required. Thus, the artisan cannot readily determine the metes and bounds of the claims based on the prior art and the guidance provided in the specification. Precise structural and/or functional features of the interactions is required.

Further as to d), chimeric peptides are recognized in the art as fusion proteins. However, the specification describes "chimeric" peptides as "peptides that do not naturally occur together in a single peptide unit", see p. 5, lines 25-p.6, line 23. Thus the breadth of the term encompasses any non-naturally occurring sequence. For example a mutated peptide by deletion, insertion or substitution combines two elements that are polypeptide fusions to make a single non-naturally occurring compound. If the claims are definite with respect to this term, it is unclear why the cited art references are traversed as not being chimeric.

Appellants argue that the artisan could determine that an aggregate forming domain refers to the amino acids of an aggregate-prone amyloid protein that are involved in aggregation. However, there is no basis for the importation of such meaning to the claims. Appellants suggest that the embodiment in which the N-terminal domain of SUP 35 has been replaced with 1-42 of beta-amyloid protein eliminates any indefiniteness of what constitutes an aggregate forming domain and that the experimentation to determine such is not undue. Yet, the specification fails to provide the structural constraints of the domain and fails to clarify the functional requirements of

the required "aggregation". The artisan is not immediately apprised of the particular meaning of the claim, an assay for measuring it or any indication of the residues that are comprised within it and thus the metes and bounds of the domain remain indefinite. It is unclear whether Appellants regard residues 1-42 of beta-amyloid as sufficient, exemplary or required.

In short the multiple uses of the terminology as set forth in the specification and art serves to cloud their meaning as intended in the claims. Thus, clarification of the metes and bounds of the terms is required.

Issue I, Appellants argue that the references do not anticipate or render obvious the claimed invention as there is no motivation to combine the references. In particular Appellants argue that the references do not teach the claimed method in yeast. In response each of the references of Hughes, Cordell and Findeis teach expression in yeast as set forth above in the 102 rejections of record. In addition, motivation to use the teachings of King and Selvaggini are provided in that King and Selvaggini each teach measurement of aggregation of aggregate prone amyloid proteins via protease resistance assay. Thus, the method of achieving the claimed results is disclosed in King and Selvaggini and the artisan would recognize the alternative procedure as an equivalent. Thus, motivation is provided as set forth.

Issue J, Appellants argue that the Hughes and Findeis references do not anticipate or render obvious the claimed invention. The claimed method is taught in yeast cells as set forth in the 102 rejection of record. Further the references are

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directed to chimeric proteins with a means for detection. Motivation is provided as Ogawa, Schilthuis and Mohler teach the success of particular fusion partners for detection. In particular chimeric fusion marker proteins for the glucocorticoid receptor as taught by Ogawa, the thyroid hormone receptor as taught by Schilthuis or a drug resistance marker protein as taught by Mohler are established as suitable for the detection of/as a marker of aggregation. One of skill in the art would have been motivated to make such modification based on the suitability of the peptides as used for detection, the positive results achieved and the expectation of positive results using the fusion partners in detection assays as taught by the exemplary teachings of Ogawa, Schilthuis and Mohler. Thus, motivation is provided as set forth.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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February 19, 2003

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